REMARKS

Claims 1-2, 18-19, 23-36, and 46-69 were pending in this application. Applicants propose to cancel claims 1-2, 18-19, 23-36, and 46-62, amend claims 63-69, and add new claims 70-78. The amendments to claims 63-69 and new claims 70-78 are supported in the application, e.g., at pages 13-14 and 19-23. Thus, these amendments and new claims would add no new matter. If the proposed amendments are entered, claims 63-78 would be pending.

Applicants submit that the proposed amendments present rejected claims 63-69 in better form for consideration on appeal, cancel all other claims, and add new claims 70-78, which are variations of pending claims 63 to 69. Thus, applicants respectfully submit that the proposed amendments be entered.

Applicants thank the Examiner for the telephone conference on October 13, 2004, in which the Examiner indicated that he would consider applicants' proposed claim amendments. The undersigned and the Examiner discussed then pending claims 63 to 69 and the proposed new claims. Applicants thank the Examiner for his willingness to consider the present Response.

35 U.S.C. § 103

Claims 1, 2, 18, and 19 have been rejected as allegedly unpatentable over McKay *et al.* (US Patent No. 5,877,309) in view of Gupta *et al.* (EMBO Journal, 15:2760-2770, 1996) and Sawyer *et al.* (Molecular Biology and Biotechnology, A Comprehensive Desk Reference, Ed. Robert A. Myers, pages 648-653, Wiley-VH, USA, 1995). Claims 1, 2, 18, and 19 have been canceled, thereby obviating this rejection.

Claims 49-59 have been rejected as unpatentable over Gupta and McKay. Claims 49-59 have been canceled, thereby obviating this rejection.

Claims 23-36, 46-48, and 60-69 have been rejected as unpatentable over Gupta, Schwarzschild *et al.* (J. Neuroscience, 17:3455-3466, 1997), and Meldrum (Brain Research Reviews, 18:293-314, 1993). Claims 23-36, 46-48, and 60-62 have been canceled, obviating this rejection with respect to those claims. This response will focus on the rejection as it pertains to claims 63-69, which are still pending.

The claimed invention relates to methods for identifying a compound that modulates excitotoxicity by studying compounds that modulate JNK3 expression or activity. The methods can be performed in a cell or in an animal model of excitotoxicity. They can also include the use of a control cell. The compounds can, for example, decrease excitotoxicity, reduce JNK3 expression, or reduce JNK3 activity, such as JNK3 substrate binding. The compounds can be, for example, a soluble peptide, a phosphopeptide, a peptidomimetic, a small organic molecule, or an inorganic molecule.

Applicants respectfully submit that the cited references fail to suggest or motivate their combination, and fail to provide a reasonable expectation of success of the presently claimed invention. Applicants will first discuss the references in combination and then discuss each reference in more detail.

The Office Action states (page 11):

> Combining the teachings of the above three references it would have been obvious to one of ordinary skill in the art that glutamate is an excitotoxin capable of inducing several types of neuronal damage and over stimulation by high levels of glutamate would also activate JNK kinase including JNK3 which phosphorylates other transcriptional factors and therefore, compounds which inhibit JNK activities such as phosphorylation, binding, etc. would in turn inhibit excitotoxic effects of glutamate or related amino acids and that such compounds could be identified by administering a compound which inhibits JNK3 expression/activity *in vitro*, to an animal model of excitotoxic disorder as taught by Meldrum and choosing those that reduce the excitotoxic effects.

Applicants respectfully disagree. In light of the three references, it would not have been obvious to one of skill in the art to carry out a method of identifying a compound that modulates excitotoxicity by incubating a cell that can exhibit excitotoxicity with a compound that modulates JNK3 expression or activity under conditions and for a time sufficient for the cell to express exhibit excitotoxicity in the absence of the compound. The cited references also fail to suggest a method of administering a compound that modulates JNK3 activity or expression to an animal model of an excitotoxicity disorder. The Office Action fails to support a prima facie case of obviousness; there are simply too many unsupported mental "leaps" to connect these disparate references as suggested in the Office Action.

In general, applicants note that Gupta makes no mention of a potential role for glutamate in any biological process; the reference uses interleukin-1 treatment to activate the JNK kinases. Schwarzschild states that the authors saw no excitotoxicity when they administered glutamate to striatal neurons. In addition, Meldrum discloses that glutamate has not been shown to cause any neuropathology, such as excitotoxicity, in any model other than neonatal rodents. Thus, it would not have been obvious to carry out the claimed methods.

In particular, there is no suggestion to combine the references to achieve a method of assaying JNK3's role in mediating excitoxicity. Although stimulation by high levels of glutamate may lead to activation of JNK kinases, which may cause phosphorylation of other transcriptional factors, it does not necessarily lead to excitotoxicity. Gupta uses interleukin-1, not glutamate, to activate JNK kinases. Schwarzschild discloses that glutamate treatment leads to activation of the JNK kinases, but states that the cells exhibited no toxicity during the course of the experiments. Meldrum makes no mention of JNK kinases. Thus, a person of ordinary skill in the art, in reading these references, would have had no motivation or suggestion to examine the role of JNK kinases, much less JNK3, in mediating excitotoxicity.

The Office Action also states (page 11):

> One of ordinary skill in the art would have been motivated to do so [the claimed invention] as such identified compounds would be expected to have use as therapeutic agents for excitotoxic disorders. One of ordinary skill in the art would have a reasonable expectation of success since Meldrum teach the animal model experiments, Gupta *et al.* teach the assay methods to monitor for JNK activity/expression/binding and phosphorylation and Schwarzschild *et al.* show the connection between glutamate and JNK.

Again, applicants respectfully disagree, because the references themselves do not provide the requisite motivation to practice the claimed invention. Applicants submit that the three references cannot be combined as suggested in the Office Action, and even if combined do not describe the invention of the amended claims. The cited references do not disclose a connection between JNK3 and excitotoxicity and fail to describe or suggest the claimed screening methods. Instead, it appears that the alleged motivation comes from the present application, not from the

prior art. As the Examiner is no doubt aware, it is improper to use the application as a roadmap to combine different references.

Gupta describes methods for assaying JNK kinase binding and JNK kinase target phosphorylation, but does not describe assays to measure excitotoxicity. Schwarzschild also does not teach assays for measuring excitotoxicity. Meldrum discloses animal models, but fails to disclose anything at all about JNK3. The references would not have provided a reasonable expectation of success or have led a person having ordinary skill in the art to study the role of JNK kinases, specifically JNK3, in excitotoxicity.

Applicants now address the characterization of each of the references cited in the Office Action.

The Office Action states at page 10:

> Gupta *et al.* teach the isolation of nearly 10 different isoforms of JNK proteins from human brain cDNA library and subclone those cDNAs in CHO cells. The reference also teaches the isolation and characterization of JNK1, JNK2 and JNK3 and specific assays for activity (result of expression of JNK), assays to determine binding of the substrate and phosphorylation of the substrate. However, the reference does not teach method to identify compounds that modulate the above activities using the very same assays or the role of JNK3 in excitotoxicity.

The Office Action concedes that Gupta does not teach methods to identify compounds that modulate JNK3 activities such as binding and phosphorylation or the role of JNK3 in excitotoxicity using the very same assays. Claims 63-69 have been amended to cover methods used to determine which compounds that modulate JNK3 also modulate excitotoxicity. Gupta does not identify compounds that modulate JNK3 expression or activity or teach how to assay whether a compound is a modulator of excitotoxicity.

Furthermore, the reference does not disclose or even suggest that JNK3, or any JNK kinase, has a role in excitotoxicity. Gupta suggests that the various isoforms of JNK kinases may have differing roles, but does not give any motivation or suggestion to focus studies on JNK3 or of a potential role for JNK3 in affecting excitotoxicity. Gupta describes on pages 2760, 2761, and 2762 that JNK kinases can activate several transcription factors, such as ATF2, Elk-1, and c-

Jun, and states, "[t]he purpose of these studies was to define the JNK isoforms ... and to examine the specificity of the interaction of these protein kinases with signal transduction targets" (page 2761). Gupta also states, "the lack of correlation between the observed binding and phosphorylation indicates that these are separate attributes of the JNK interaction with the Jun family proteins. This analysis raises questions about the physiological function of the JNK binding interaction" (pages 2767-2768). In addition, the reference states, "JNK isoforms may have different binding specificities" (page 2761). Thus, it would not have been obvious to a person of ordinary skill in the art that a compound that modulates one JNK kinase or one JNK function (e.g., binding of a target) would inhibit another JNK kinase or function (e.g., phosphorylation or excitotoxicity).

Next, the Office Action states:

> Schwarzschild *et al.* teach the role of glutamate in its stimulation of JNK proteins in striatal neurons. The reference teaches that glutamate, which is well recognized in the art as an excitatory amino acid raises the levels of phosphorylated JNK, in other words activates JNK kinases which is mediated by NMDA receptors. The reference also reports the involvement of JNK pathway in glutamate-regulated developmental, neurodegenerative and neurotoxin processes in the CNS. Thus Schwarzschild *et al.* link glutamate stimulation with activation of JNK kinases. The reference does not specifically recite that JNK3 is activated. However, Examiner takes the position that all JNK isoforms are encompassed in the above reference.

Schwarzschild states that glutamate treatment of neonatal striatal neurons leads to activation of JNK kinases. However, this reference does not teach a connection between JNK kinases and induction of excitotoxicity, motivate one to study the effects of JNK kinases on excitotoxicity, or provide a reasonable expectation of success in carrying out the claimed methods. On page 3464, Schwarzschild states that a role for glutamate in neurotoxicity has been observed and that a potential role for JNK in this process was considered. But the reference goes on to state, "[h]owever, glutamate at a concentration of 100 μM, which maximally activates SAPK/JNK (Fig. 7A), *does not produce signs of cellular toxicity or death in our striatal cultures*. Other have also reported *minimal or no toxicity of glutamate* in similar short-term cultures of striatal neurons" (page 3464) (emphasis added). These observations teach away from

modulating JNK kinase activity to achieve modulation of excitotoxicity, and thus support the notion that the prior art does not provide a reasonable expectation of success for the claimed methods.

The Office Action seems to overstate the relevance of Schwarzschild's disclosure. The reference does not "report[] the involvement of JNK pathway in glutamate-regulated developmental, neurodegenerative and neurotoxin processes in the CNS" because, at best, Schwarzschild presents a *hypothesis* that JNK kinases may be involved in such processes by stating, "our data raise new questions regarding the involvement of SAPK/JNK pathways in glutamate-regulated developmental, neurodegenerative, and neurotoxic processes in the CNS" (page 3456) (emphasis added) and, "[o]ur findings also raise the possibility that SAPK/JNK ... plays a role in physiological and pathological effects of glutamate ... These results ... lead to the hypothesis that SAPK/JNK may mediate the glutamate-induced cell death implicated in both normal neural development and neurodegenerative disease" (page 3464) (emphasis added). These mere questions do not support the Office Action's characterization of Schwarzschild and, more importantly, fail to provide a person with ordinary skill in the art with a reasonable expectation that modulation of JNK kinase activity or expression levels would result in modulation of excitotoxicity.

The Office Action also states:

> Meldrum teaches in detail amino acids that act as excitotoxins and their contribution to neurodegenerative disorders. On page 304 the reference provides *in vivo* studies of excitotoxicity and provides different techniques and methods of monitoring excitotoxic effects. Under retinal pathology method, the reference teaches a mouse model (neonatal mice) using high doses of glutamate. The reference also teaches the toxicity caused by kainic acid which for all practical purposes is highly similar to glutamate in its excitotoxicity (see page 297).

Meldrum describes methods to study excitotoxicity in animal models, but fails to describe how to select or identify which compounds to test for modulation of excitotoxicity. In contrast, the claimed invention teaches testing compounds that modulate JNK3 for modulation of excitotoxicity. Also, only claims 71 and 72, and claims depending from them use animal models so Meldrum's teaching of animal models does not pertain to the claimed methods that use cell-

based assays. Meldrum fails to teach an element of claims 63, 70, 71, 72, and the claims depending from them.

Meldrum does not disclose or suggest a connection between glutamate, JNK3 or any JNK kinase, and excitotoxicity. Also, it states that the mechanisms by which glutamate acts vary: "It is clear that glutamate ... can be cytotoxic in culture *by a mechanism not involving excitotoxicity*" (page 302) (emphasis added). The Examiner has cited Schwarzschild as allegedly supplying the missing link between Gupta and Meldrum, but this link fails, because Schwarzschild expressly states that glutamate at the relevant JNK activating dosage does not produce signs of cellular toxicity or cell death in culture.

Thus, taken together, none of the cited prior art references describes a connection between JNK kinase activation and excitotoxicity, and the prior art references are silent as to the mechanism of the underlying signaling events. It is entirely possible that glutamate triggers excitotoxicity and JNK kinase activation through two different and independent signaling pathways, in which case JNK kinase activation may have no effect on excitotoxicity. It is also possible that JNK kinase activation is a consequence of excitotoxicity, in which case modification of JNK kinase activity may also be without effect on excitotoxicity. Thus, a person having ordinary skill in the art would not have reasonably expected that modulation of JNK kinase activity or expression levels would result in modulation of excitotoxicity. Consequently, it could not have been obvious to screen modulators of JNK kinase activity for their effect on excitotoxicity, and applicants submit that the Office Action has failed to establish a prima facie case of obviousness.

CONCLUSION

Applicants respectfully request that the Examiner cancel claims 1-2, 18-19, 23-36, and 46-62, enter the amendments to claims 63-69, enter new claims 70-78, and allow claims 63-83.

Enclosed is a $980.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney's Docket No. 10363-005001.

Respectfully submitted,

Date: 11-01-2004

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